REMARKS/ARGUMENTS

Interview

Applicants appreciate the opportunity to discuss the new matter rejection with Examiner Myers on September 9, 2008. Applicants asked whether the Examiner could suggest any amendments that would address the rejection, and she responded that she could not. Applicants pointed out that the mutant rhodopsin recited in the claims was used as a control in Example 1, and that one of skill would therefore understand that this mutant rhodopsin would be a useful control in other assays, including the claimed screening assays. The Examiner stated that the understanding of one of skill in the art is not the standard for possession, and that, because the specification does not specifically describe the mutant rhodopsin being used in a screening assay, the presently claimed methods lack written description.

Status of the claims

Claims 1, 5-13, 15, 17, 19, 20, and 22 are pending. Claims 1 and 15 are amended. Support for the amendments is found throughout the claims and specification as filed. Specific support for detecting the RDGC GPCR phosphatase activity of a Rh1Δ356 mutant rhodopsin is found, *e.g.*, on page 44 and Figure 1B. A mutant rhodopsin comprising wild type rhodopsin lacking the last 18 amino acids at the carboxy-terminus is found, *e.g.*, on page 4, lines 10-11 and page 44. Support for the concept of a control sample is found, *e.g.*, on page 9, lines 19-21, page 22, lines 28-31, and in the examples.

Rejection under 35 USC § 112, first paragraph - New matter

The Examiner has rejected claims 1, 5-13, 15, 17, 19, 20, and 22 as allegedly failing to comply with the written description requirement, and in particular, the proscription against new matter. According to the Examiner, the specification does not provide a basis for a method of screening that comprises a step of providing a second sample comprising a mutant rhodopsin lacking the last 18 amino acids at the cytoplasmic terminus.

In the Advisory Action, the Examiner indicates that the Amendment filed July 8, 2008 has not been entered, but provides some comments on the substance of the Amendment. In particular, the Examiner asserts that the rejection is not based on the obviousness of including a control such as the R1Δ356 mutant in a screening method, but that the specification does not particularly describe use of the R1Δ356 mutant in a screening method. The Examiner also indicates that the recited mutant rhodopsin encompasses mutants with more than 18 amino acids deleted from the C-terminus. To the extent the rejection applies to the amended claims, Applicants traverse.

The Invention

The invention is directed to methods of screening for compounds that modulate RDGC GPCR phosphatase activity, wherein the method comprises comparing the functional effect of a test compound under experimental conditions to that of a control. As explained below, one of skill reading the present specification would readily recognize the inventors' possession of the recited control sample for a screening method.

Legal Standard

The legal standard for written description is one of reasonableness, *i.e.*, whether a skilled artisan would reasonably believe that the inventors had possession of the claimed invention as of the filing date. As explained in the MPEP § 2163, "the proscription against the introduction of new matter in a patent application serves to prevent an applicant from adding information that goes beyond the subject matter originally filed." The MPEP continues, "there is no *in haec verba* requirement, and newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure."

Sufficiency of disclosure is discussed in *In re Chilowsky*, 108 USPQ 321 (CCPA 1956). The court was addressing whether claims involving energy transport in a nuclear reactor were indefinite and/or inoperable. The issue, however, was similar to the one raised here, *i.e.*, what is meant by sufficient disclosure. The court stated, "an application embraces not only what

is expressly set forth..., but what would be understood by persons skilled in the art. ... [T]hat which is common and well known is as if it were written out in the patent." *Id.* at 325. The court acknowledged that many of the procedures and materials were described in general terms, but found that it would be fatal only if those of skill in the art did not possess the necessary knowledge to make the required determination. *Id.* at 326.

The Federal Circuit addressed sufficient disclosure in the context of the written description requirement in *Moba B.V. v. Diamond Automation, Inc.*, 66 USPQ2d 1429 (Fed. Cir. 2003). The court reviewed its case law, and explained that the written description requirement does not require the application to describe exactly the subject matter claimed as long as one of skill would recognize that the inventor invented what is claimed. *Id.* at 1469. The court found that the claims at issue were adequately described because every element of the claim was disclosed in sufficient detail to allow this recognition. *Id.* In *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 2001), the court emphasized the case-specific nature of the inquiry, stating, "it should be readily apparent from recent decisions of this court involving the question of compliance with the description requirement of §112 that each case must be decided on its own facts."

The Present Disclosure is Sufficient to Convey Possession

The claims are drawn to methods of screening for RDGC GPCR phosphatase modulators. The specification describes materials and assays for such methods, *e.g.*, in the section beginning on page 22. Line 26 of page 22 states that modulation can be tested using one of the *in vitro* or *in vivo* assays described herein.

The examples describe assays for determining RDGC GPCR phosphatase activity, in particular, in retinal cells exposed to blue light or orange light conditions. Rhodopsin (Rh1), the substrate for RDGC phosphatase, is phosphorylated in blue light, and then dephosphorylated in orange light by RDGC phosphatase. If Rh1 is not dephosphorylated, it is not properly deactivated, and retinal degeneration occurs. The examples include various conditions for comparison to normal RDGC phosphatase activity, in order to demonstrate the full extent of its

phosphatase activity on Rh1. These comparisons include: blue light (RDGC phosphatase not activated); blue followed by orange light (RDGC phosphatase active); a mutant, inactive RDGC phosphatase (rdgC); a sample with no RDGC phosphatase substrate (NinaE), and a sample with mutant RDGC phosphatase substrate (R1Δ356). R1Δ356 represents defective substrate for RDGC phosphatase, as it lacks the particular residues that were believed to be phosphorylated in blue light and then dephosphorylated by RDGC phosphatase in orange light (*see* page 44, lines 12-14).

Example 1 is directed to detecting RDGC GPCR phosphatase activity, but does not describe a method of screening for modulators of that activity. However, the example does include conditions with the inactive RDGC phosphatase (rdgC), which is analogous to a condition with a RDGC phosphatase inhibitor. Example 1 thus provides a side-by-side comparison of wild type Rh1 and mutant Rh1 (R1Δ356), with either normal RDGC phosphatase (Figure 1B, lanes 1 and 5) or inactive RDGC phosphatase (Figure 1B, lanes 4 and 6). A skilled molecular biologist, familiar with the concept of controls, would understand that the mutant rhodopsin is used in Example 1 to ensure that the changes in phosphorylation of Rh1 (indicative of RDGC GPCR phosphatase activity) is entirely due to phosphorylation and dephosphorylation at the expected C terminal residues.

The word "control" is not used in Example 1, but the purpose of the sample is clear. The Rh1Δ356 sample is used to ensure that only the relevant phosphorylation of rhodopsin, *i.e.*, the phosphorylation occurring at the carboxy-terminus, is considered. A careful comparison of Figure 1B lanes 1 and 5, and then lanes 4 and 6, indicates that the mutant rhodopsin is phosphorylated to a small extent in the blue light condition, and dephosphorylated in the orange light condition, even in the absence of RDGC phosphatase. This effect must be subtracted when considering the results for wild type rhodopsin, or one would not be "detecting the level of Drosophila RDGC GPCR phsphatase activity." The comparative value of the Rh1Δ356 sample is consistent with the concept of a control as it is understood in the art.

The skilled molecular biologist considering a screen for modulators of RDGC GPCR phosphatase, would understand that any screening method would require appropriate

controls. Moreover, this person of skill would recognize that the controls described in Example 1, could be applied to a method of screening.

Regarding sufficiency of disclosure, one of skill would recognize that the inventors understood the concept of controls, and thus had possession of the presently claimed methods. Page 22 of the specification describes exemplary controls for testing modulators of RDGC GPCR phosphatase activity (beginning at line 27). Page 9, lines 18-21, provides an additional exemplary control for a screening assay. While these control samples are not the same as that recited in the claims, one of skill would certainly recognize that the inventors knew (i) that screening assays require controls, and (ii) that a control sample with Rh1Δ356 would be an appropriate comparison in assays for RDGC GPCR phosphatase activity. The specification therefore complies with the written description standard recited in *Moba*, as it describes every element of the claimed methods so that one of skill would recognize the inventors' possession of the same.

Finally, solely in an effort to expedite prosecution, Applicants have amended the description of the mutant rhodopsin recited in claims 1 and 15 to address the concern that the mutant could lack more than 18 amino acids from the C terminus. The mutant rhodopsin is now described as "comprising wild type rhodopsin lacking the last 18 amino acids at the carboxy-terminus." The word "comprising" in the amended phrase indicates that the mutant rhodopsin is at least as long as the wild type lacking 18 amino acids, but not shorter.

As reviewed above, the standard for sufficient disclosure is one of reasonableness, not precise "*in haec verba*" support. Thus, while the word "control" does not appear in Example 1, it is not required for compliance with the disclosure requirement. The assertion that one reading the present specification, which is focused entirely on signal transduction and commonly-used assays, would not appreciate the inventors' possession of a control sample does not comply with the reasonableness standard. This is especially true considering that use of the recited control is described in the specification. Accordingly, Applicants submit that the claimed methods are sufficiently disclosed, and respectfully request withdrawal of the rejection under the first paragraph of 35 USC § 112 for new matter.

Rejection under 35 USC § 112, second paragraph

The Examiner has rejected claims 1, 5-13, 15, 17, 19, 20, and 22 as allegedly indefinite. According to the Examiner, the claimed methods do not utilize the "second sample" in any of the recited methods. In addition, the Examiner contends that the language of "detecting a change" in activity is unclear because the claims do not recite what is being compared.

In the Advisory Action, the Examiner indicates that the Amendment filed July 8, 2008 has not been entered, but provides some comments on the substance of the Amendment. In particular, the Examiner asserts that the amendment raises issues because it does not state whether steps iii) and v) are the same or separate steps. The Examiner also states that the claims do not set forth how detecting RDGC GPCR phosphatase activity in the first and second samples results in determination that a test compound is a modulator.

Solely in an effort to expedite prosecution, Applicants submit amended claims 1 and 15. As amended, the claimed methods clarify that the level of RDGC GPCR phosphatase activity is detected in both before and after the addition of a test compound. Thus, the amended claims make clear that the second sample is utilized in the claimed methods.

Applicants respectfully submit that the same amendment addresses the assertion that the claims do not set forth how the recited detection results in determination of modulating activity. If the RDGC GPCR phosphatase activity in the first sample is different between step (iii) and step (v), once the background level from the second sample is considered, then the test compound is a modulator of RDGC GPCR phosphatase activity.

In view of the amendments to the claims and foregoing comments, Applicants respectfully request withdrawal of the rejections under the second paragraph of 35 USC § 112.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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